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Epidemiology of and risk factors for mortality due to carbapenemase-producing organisms (CPO) in healthcare facilities

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Background: Carbapenemase-producing organisms (CPO) have been largely responsible for the extensive spread of carbapenem resistance, and their prevalence is increasing in many parts of the world.
Aim: To evaluate clinical and molecular epidemiology and mortality associated with CPO among patients.
Methods: All CPO from clinical and long-term healthcare surveillance cultures across Scotland in 2003–2017 were reviewed retrospectively. Polymerase chain reaction was used to detect genes coding for carbapenemases. A generalized linear mixed model was used to identify risk factors for mortality.
Findings: In total, 290 individuals with CPO were identified. The overall incidence increased over time ($P<0.001$) from 0.02 to 1.38 per 100,000 population between 2003 and 2017. A total of 243 distinct CPO isolates were obtained from 269 isolations in 214 individuals with available metadata. The majority of the isolates were Enterobacterales (206/243, 84.8%), and *Klebsiella pneumoniae* (65/206, 31.6%) and *Enterobacter cloacae* (52/206, 25.2%) were the most common species. VIM (75/243, 30.9%) and NDM (56/243, 23.0%) were the most common carbapenemases. The crude 30-day mortality rate was 11.8% (25/211), while the case fatality rate was 5.7% (12/211). Age >60 years [adjusted odds ratio (aOR) 3.36, 95% confidence interval (CI) 1.06–10.63; $P=0.033$], presence of non-

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fermenters (aOR 4.88, 95% CI 1.64–14.47; P=0.005), and systemic infection or organ failure (aOR 4.21, 95% CI 1.38–12.81; P=0.032) were independently associated with 30-day mortality.

Conclusion: The incidence of CPO in Scotland is low but increasing. Awareness is required that inpatients aged >60 years, patients with systemic infection or organ failure, and patients presenting with non-fermenters are at higher risk of death from CPO.

Introduction

Over the past two decades, the emergence of carbapenem-resistant organisms (CRO) has become a global public health crisis, leaving few effective therapeutic options available to treat multi-drug-resistant infections [1,2]. Resistance to carbapenems arises from two general mechanisms: carbapenemase production and non-enzymatic. CRO strains that do not produce carbapenemases (non-enzymatic) are usually less resistant to other antibiotics [3], and their carbapenem resistance trait is not transferable. Carbapenemases, in contrast, are encoded by genes frequently carried on mobile genetic elements such as plasmids and transposons, which could be transferred between different species and individuals. Therefore, carbapenemase-producing organisms (CPO) have largely been responsible for the rapid and extensive worldwide spread of CRO, and are considered to be of more clinical concern than non-enzymatic CRO.

With regard to the epidemiological stage of CPO, the UK is reported to be in a 'regional spread' situation, while many European countries are in an 'inter-regional spread or endemic' situation, such as Italy, Greece, France, Poland and Denmark [4]. In the UK, the prevalence and incidence of clinically significant CPO is currently low, but these multi-drug-resistant bacteria affect most UK regions [5]. In Scotland, the first CPO was reported in an *Enterobacter cloacae* complex blood culture isolate in 2003, carrying *Klebsiella pneumoniae* carbapenemase-4 [6]. The prevalence of CPO in Scotland (0.1 per 100,000 patient-days) was lower than that in England and Northern Ireland (0.85 per 100,000 patient-days) in healthcare settings [7]. However, there has been a 39% year-on-year increase in the prevalence of reported CPO isolates since 2013 in Scotland, from 0.4 per 100,000 population in 2013 to 2.0 per 100,000 population in 2017 [8]. The epidemiology of Scottish CPO isolates, however, remains unclear. As such, this study aimed to conduct a detailed analysis of epidemiological characteristics of CPO in Scotland. Insights based on these findings will further the development of effective and appropriate prevention and infection control strategies, thus contributing to curb future emergence and spread of CPO in Scotland.

Methods

Ethics

All data for analyses in this study were anonymized. The study was reviewed and approved by the Public Benefit and Privacy Panel for Health and Social Care, and covered by National Safe Haven generic ethics approval (Ref. No. 1617–0328). The study was conducted in accordance with the Declaration of Helsinki, and national and institutional standards.

Study design

A national retrospective observational study was conducted among patients in Scotland between January 2003 and December 2017. Specimens with suspected CPO from clinical indications or a surveillance programme were submitted to a Scottish diagnostic laboratory. Identification of isolates and antimicrobial susceptibility tests were performed using VITEK®2 (bioMérieux, Marcy-l'Étoile, France) [5]. If the isolate was non-susceptible to at least one carbapenem, the diagnostic laboratory referred the isolate to the Antimicrobial Resistance and Healthcare-Associated Infections (AMRHAI) Reference Unit at Public Health England (PHE) for confirmation of carbapenemase production by in-house polymerase chain reaction [5].

Definitions

In this article, samples have been described as cases, isolations and isolates. A CPO case was defined as an individual from whom there has been a CPO isolation. Each CPO isolation was described on the basis of organism (e.g. *K. pneumoniae*), enzyme (e.g. VIM), isolation date and specimen (e.g. urine). Isolations that differ in any of these characteristics represented different isolations. For each CPO case, a CPO isolate was defined on the basis of organism and enzyme; a difference in either organism or enzyme represented different isolates. Therefore, each CPO case could contribute multiple CPO isolations with multiple CPO isolates. For one CPO case, if there were multiple isolations of the same isolate from the same specimen, only the first isolation was included in the study. This method was used in order to assess the diversity of carbapenemases and independent specimen sources for statistical analysis more uniformly. All cases were classified as healthcare-associated (HA) or community-associated (CA) [9,10] (Table S1, see online supplementary material). Specimen type of the isolations was aggregated into seven groups: urine, alimentary, wound, normally sterile site, respiratory, superficial, and site unspecified.

Data collection

The data used in this study were extracted from several national datasets. Laboratory records were extracted from the Electronic Communication of Surveillance in Scotland. Medical records at individual level were extracted from the General Acute Inpatient and Day Case – Scottish Morbidity Record.

Mortality data at individual level were extracted from the National Records of Scotland Deaths. Data extraction and linkage of these datasets were performed by Public Health Scotland via the electronic Data Research and Innovation Service (eDRIS).

Outcomes and statistical analysis

The outcomes included:

(i) incidence of CPO, defined as the number of new CPO cases per 100,000 population per year. Temporal trends in incidence were investigated using an exponential model; temporal trends in incidence of Enterobacterales and non-fermenters were explored using a generalized linear model, and differences in temporal trends in incidence between Enterobacterales and non-fermenters were examined by testing for an interaction between bacterial family and isolation year. Temporal trends in incidence of CPO source (HA and CA) and differences in temporal trends in incidence between HA and CA cases were examined as described above.
(ii) Mortality of CPO cases. Crude 30-day mortality rate, defined as the number of deaths within 30 days of CPO isolation per 100 cases; and case fatality rate (CFR), defined as the number of CPO-attributed deaths per 100 cases.
(iii) Risk factors for 30-day mortality of CPO inpatient cases. A generalized linear mixed model was used to determine the risk factors. Independent variables included demographics, microbiological characteristics, comorbidities, healthcare exposure and invasive procedures in the 90 days preceding CPO isolation. Definitions for each independent variable are listed in Table S2 (see online supplementary material).

Univariate analysis was performed first, and all variables with $P<0.10$ were carried forward for multi-variate analysis. Correlations between variables with $P<0.10$ on univariate analysis were checked by calculating correlation coefficients. Also, possible interactions between variables were checked. Model averaging was used to construct the final multi-variate model using the Akaike weights of the candidate models [11]. For statistical purposes, variables with zero values in either group were removed from multi-variate analyses. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to determine the strengths of these associations. All analyses were performed using R Version 3.3.3, and $P<0.05$ was considered to indicate statistical significance.

Results

Overview of the study

Up to the end of 2017, a total of 290 cases were diagnosed with CPO isolation from 13 of 14 Scottish National Health Service boards. The metadata of cases identified in 2003 ($N=1$) and 2017 ($N=75$) were not available, hence only 214 cases were included in the subsequent analyses. Clinical characteristics of CPO cases are listed in Table I. There were more female cases ($N=112$, 52.3%) than male cases ($N=102$, 47.7%). The age of CPO cases ranged from 0 to 92 years (median age 63 years, interquartile range 53–78 years). There was no difference in age between male and female cases ($P=0.838$). Among 214 CPO cases, 170 (79.4%) cases had a single isolation while 44 (20.6%) cases had multiple isolations, resulting in 269 unique isolations. One hundred and fifty-one (70.6%) of 214 cases were inpatients. In total, 243 CPO isolates were obtained from 214 cases. Due to incompleteness of the medical records for three CPO cases, the CPO source could be classified for only 211 cases. Among them, 149 (70.6%) were HA cases. Incidence rates of both HA and CA increased significantly over time ($P<0.001$), but no difference in temporal trends in incidence was found between them ($P=0.310$).

Incidence and mortality of CPO

Figure 1 shows the number of CPO cases and temporal trends in incidence from 2003 to 2017. Overall incidence increased between 2003 and 2017 (incidence $\sim 0.025*1.332^{year}$; $P<0.001$) from 0.02 to 1.38 per 100,000 population. To evaluate the impact of active surveillance for carbapenemase-producing Enterobacterales (CPE) introduced in August 2013, an exponential model was used to fit the data before (2003–2013) its introduction. Before surveillance, the model was incidence $\sim 0.021*1.330^{year}$. Incidence rates of Enterobacterales and non-fermenters increased significantly over time ($P<0.001$), but the prevalence of Enterobacterales (annual increase of 42.5%) increased faster than that of non-fermenters (annual increase of 21.5%) ($P=0.001$). The crude 30-day mortality rate was 11.8% (25/211) and CFR was 5.7% (12/211).

Microbiological characteristics of CPO isolates

There were 269 unique CPO isolations. Urine ($N=103$, 38.3%), alimentary ($N=55$, 20.4%) and wound ($N=42$, 16.0%) specimens predominated at aggregate level, with urine ($N=99$, 36.8%), rectal swabs ($N=45$, 16.7%) and wound swabs ($N=32$, 11.9%) being the most common specimens (Figure 2). In general, the number of CPO isolations from wound, urine and alimentary samples increased gradually. The majority of CPO isolations were from urine and alimentary samples from 2013 onwards (Figure 3). The 243 CPO isolates were represented by eight genera and 14 species; the majority were Enterobacterales (206/243, 84.8%), and *K. pneumoniae* (65/206, 31.6%), *E. cloacae* (52/206, 25.2%) and *Escherichia coli* (50/206, 24.3%) were the most common species. *Pseudomonas aeruginosa* (29/37, 78.4%) predominated among non-fermenters (Figure 4). Carbapenemases comprised VIM (75/243, 30.9%), NDM (56/243, 23.0%), KPC (43/243, 17.7%), OXA-48 (43/243, 17.7%), IMP (18/243, 7.4%), IMI (3/243, 1.2%), NDM+IMP (2/243, 0.8%), NDM+OXA-48 (2/243, 0.8%) and GES-5 (1/243, 0.4%).

Risk factors for 30-day mortality of CPO inpatient cases

There were 151 inpatient cases; of these, 23 (15.2%) died within 30 days of CPO isolation. Univariate analysis indicated that all-cause 30-day mortality was associated with advanced age, presence of carbapenemase-producing non-fermenters, sepsis, malignancy, respiratory tract infection, and systemic

Table I
Clinical characteristics of carbapenemase-producing organism (CPO) cases

Characteristics	*N* (%)[a]
Demographics	
Age (years), median (IQR, range)	63 (53–78, 0–92)
Advanced age (>60 years)	124/211 (58.8)
Gender, male	102/214 (47.7)
Comorbidities	
Certain infectious and parasitic diseases[b]	70/211 (33.2)
Sepsis	18/211 (8.5)
Copresence with other pathogens	24/211 (11.4)
Neoplasms and diseases of the blood and blood-forming organs	53/211 (25.1)
Malignancy	38/211 (18.0)
Solid	16/211 (7.6)
Haematologic	22/211 (10.4)
Anaemia	11/211 (5.2)
Endocrine, nutritional and metabolic diseases	37/211 (17.5)
Diabetes mellitus	21/211 (10.0)
With complications	8/211 (3.8)
Diseases of the circulatory system	51/211 (24.2)
Heart failure	3/211 (1.4)
Diseases of the respiratory system	53/211 (25.1)
Respiratory tract infection	33/211 (15.6)
Respiratory failure	5/211 (2.4)
Diseases of the digestive system	21/211 (10.0)
Diseases of the genitourinary system	58/211 (27.5)
Urinary tract infection	35/211 (16.6)
Renal failure	21/211 (10.0)
Diseases of the nervous system	21/211 (10.0)
Diseases of the skin and subcutaneous tissue	14/211 (6.6)
Diseases of the musculoskeletal system and connective tissue	19/211 (9.0)
External causes of morbidity	53/211 (25.1)
Injury, poisoning and certain other consequences of external causes	49/211 (23.2)
Immunocompromised status	44/211 (20.9)
Healthcare exposure	
HDU stay	58/211 (27.5)
Duration of HDU stay (days), median (IQR, range)	0 (0–1, 0–65) for 211 cases
ICU stay	45/211 (21.3)
Duration of ICU stay (days), median (IQR, range)	0 (0–0, 0–39) for 211 cases
Hospitalization	87/211 (41.2)
Duration of hospitalization (days), median (IQR, range)	8 (0–31.5, 0–91) for 211 cases
Hospital transfer	32/211 (15.2)
Ward transfer	97/211 (46.0)
Emergency admission	127/150 (84.7)
Admission from healthcare facilities	16/150 (10.7)
Surgical specialty	69/150 (46.0)
TAR (days), median (IQR, range)	6.5 (1–25, 0–91) for 150 cases
Discharge type, death	32/150 (21.3)
Discharge to healthcare facilities	18/150 (12.0)
Invasive procedures	
Any	75/211 (35.5)
Centesis	10/211 (4.7)
Ectomy	20/211 (9.5)
Transplantation	4/211 (1.9)
Catheterization	19/211 (9.0)
Urinary catheter	6/211 (2.8)
CVC	15/211 (7.1)
Dialysis or drainage	7/211 (3.3)
Endoscopic operation	17/211 (8.1)
Invasive ventilation	9/211 (4.3)
Other surgical procedures	26/211 (12.3)

(*continued on next page*)

ICU, intensive care unit; IQR, interquartile range; HDU, high dependency unit; TAR, time at risk (defined as interval between admission to hospital and CPO isolation); CVC, central venous catheter.

[a] Number of cases with the characteristic/total number of cases investigated (percentage of cases with the characteristic), unless stated otherwise.

[b] Certain infectious and parasitic diseases comprise sepsis (including septic shock), infections caused by CPO, and infections caused by other pathogens (*Clostridium perfringens*, *Clostridioides difficile*, *Streptococcus* spp., *Staphylococcus* spp, *Salmonella* spp., *Aspergillus* spp., *Candida* spp., human immunodeficiency virus, hepatitis C virus, Reoviridae).

infection or organ failure (Table II). Multi-variate analysis showed that age >60 years [adjusted odds ratio (aOR) 3.36, 95% CI 1.06–10.63; P=0.033], presence of carbapenemase-producing non-fermenters (aOR 4.88, 95% CI 1.64–14.47; P=0.005), and systemic infection or organ failure (aOR 4.21, 95% CI 1.38–12.81; P=0.032) were independent risk factors for 30-day mortality (Table II).

Discussion

According to guidance from the European Centre for Disease Prevention and Control, understanding and monitoring the local epidemiological situation is necessary to implement and refine CRO prevention and control strategies [12]. To date, no comprehensive epidemiological study of CPO has been conducted in Scotland at national or individual level. To the authors' knowledge, this is the first epidemiological study of CPO in Scotland since it was first reported in 2003.

To date, there is no acknowledged definition of an episode or de-duplication criterion for a CPO case. The longest interval between isolations with the same organism and

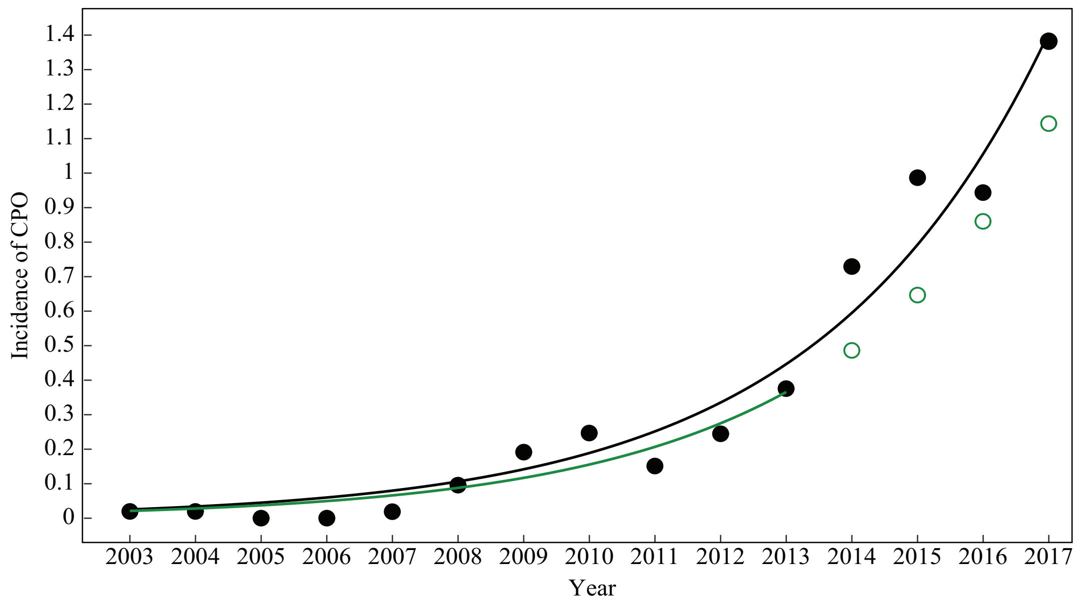

Figure 1. Incidence of carbapenemase-producing organisms (CPO) in Scotland 2003—2017. Black circles represent the incidence of CPO, and black lines represent the temporal trend in CPO incidence between 2003 and 2017. Green lines represent the temporal trend in CPO incidence before conduction of Scottish carbapenemase-producing Enterobacterales active surveillance (i.e. between 2003 and 2013), and green circles indicate the predicted incidence of CPO between 2014 and 2017 from the pre-surveillance model (2003—2013). The vertical distance between black circles and green circles represents the difference between actual incidence and predicted incidence from the pre-surveillance model between 2014 and 2017.

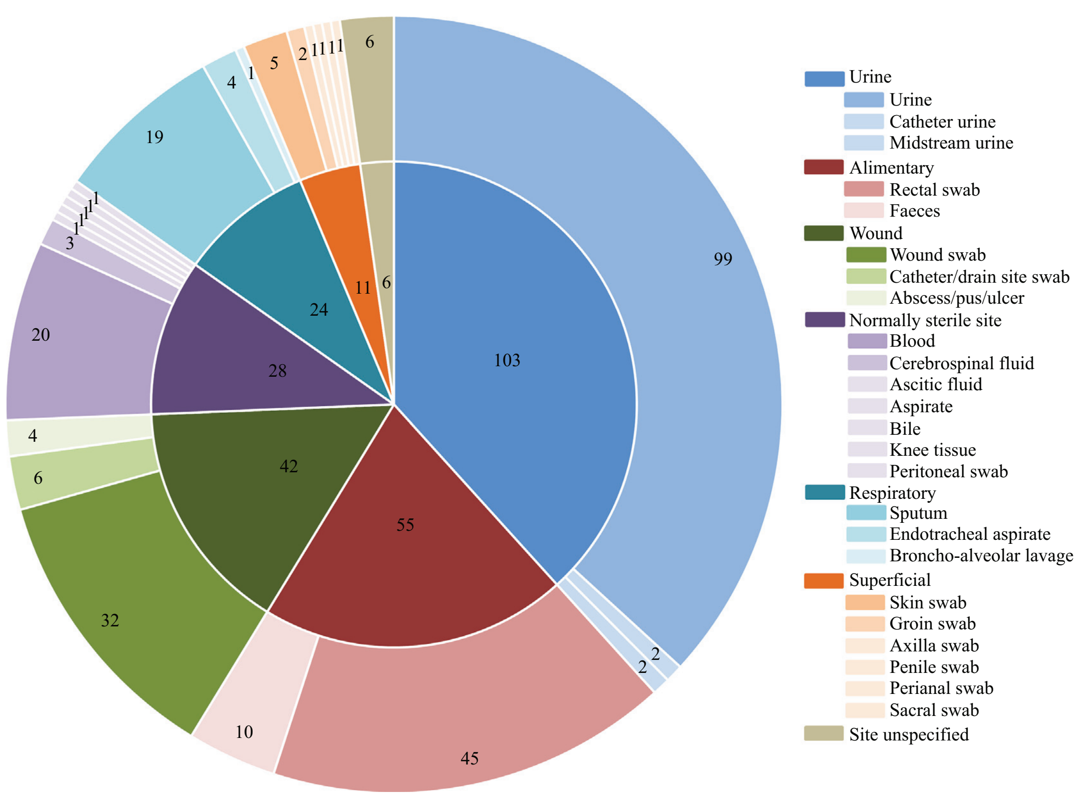

Figure 2. Specimen types of 269 carbapenemase-producing organism (CPO) isolations according to aggregate specimen (inner circle) and specific specimen (outer circle).

Figure 3. Temporal distribution of aggregate specimen types of 269 carbapenemase-producing organism (CPO) isolations.

carbapenemase from the same individual was 740 days in this study, indicating possible long-term persistence of CPO. As a result, no definition of episodes was attempted in this study, and the analysis was based on patients (i.e. CPO cases), using the first isolation for patients with multiple CPO isolations, unless stated otherwise. In 2013, Scotland launched an acute hospital admission screening programme for CPE [13]. However, carbapenemase-producing non-fermenters from CPE screening samples were also reported to Public Health Scotland and included in this study. Therefore, the subsequent increase in CPO cases reported, particularly CPE, may reflect increased awareness and testing due to the introduction of CPE screening, noting that: (i) the true incidence was higher than the extrapolations from the model in 2003—2013 (Figure 1); (ii) the incidence of Enterobacterales increased significantly faster than that of non-fermenters; and (iii) most of the isolates were from alimentary and urine samples which were usually used for screening, and the number of isolates from these specimens increased from 2013 (Figures 2 and 3). The prevalence of CPO may have been underestimated as only approximately three-

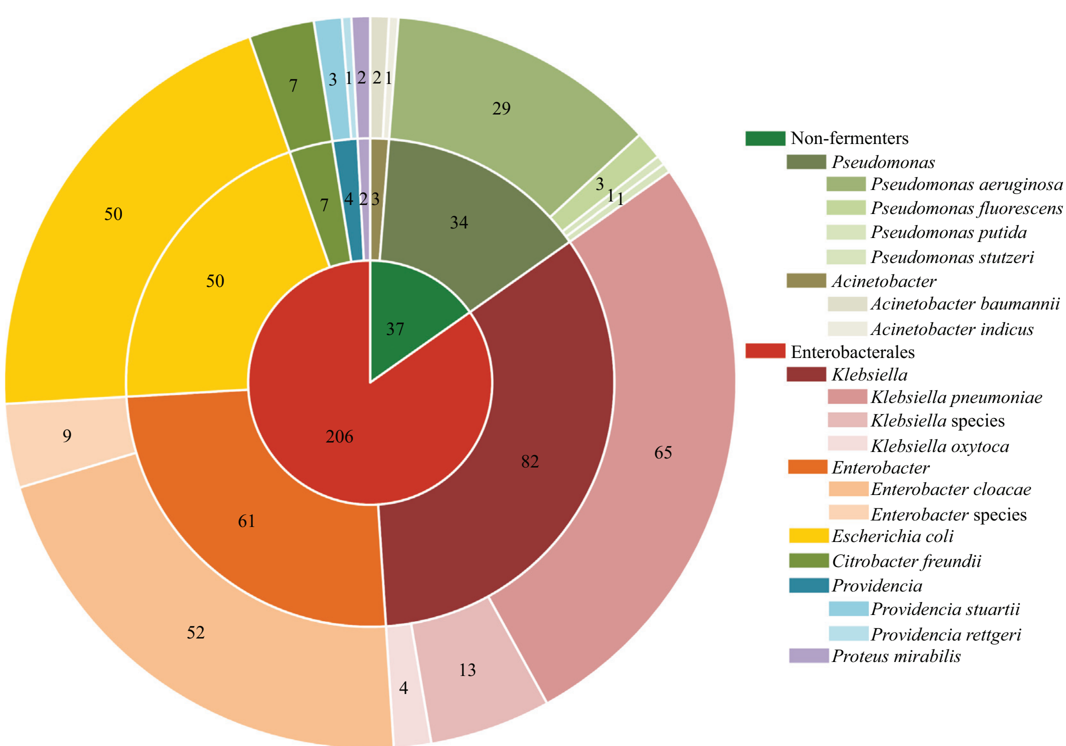

Figure 4. Family (inner circle), genus (middle circle) and species (outer circle) of 243 carbapenemase-producing organism isolates.

Table II
Characteristics associated with all-cause 30-day mortality of 150 inpatient carbapenemase-producing organism (CPO) cases

Characteristics	Survivor (%)[a] (N=127)	Non-survivor (%)[a] (N=23)	Univariate		Multi-variate	
			OR (95% CI)	P-value	aOR (95% CI)	P-value
Demographics						
Age (years), median (IQR)	62 (49.5—74)	71 (61—78)	1.04 (1.00—1.07)	0.024		
Age >60 years	69 (54.33)	18 (78.26)	3.03 (1.06—8.65)	0.039	3.36 (1.06—10.63)	0.033
Gender, male	73 (57.48)	12 (52.17)	0.81 (0.33—1.97)	0.637		
Microbiological characteristics						
Organism family, non-fermenter	21 (16.54)	10 (43.48)	3.88 (1.50—10.02)	0.005	4.88 (1.64—14.47)	0.005
Comorbidities						
Certain infectious and parasitic diseases	57 (44.88)	8 (34.78)	0.65 (0.26—1.65)	0.371		
Sepsis	11 (8.66)	6 (26.09)	3.72 (1.22—11.38)	0.021		
Co-presence with other pathogens	20 (15.75)	1 (4.35)	0.24 (0.03—1.91)	0.179		
Neoplasms and diseases of the blood and blood-forming organs	37 (29.13)	10 (43.48)	1.87 (0.75—4.64)	0.177		
Malignancy	24 (18.90)	9 (39.13)	2.76 (1.07—7.12)	0.036	1.57 (0.49—5.09)	0.081
Solid	8 (6.30)	3 (13.04)	2.23 (0.55—9.13)	0.264		
Haematologic	16 (12.60)	6 (26.09)	2.45 (0.84—7.13)	0.100		
Anaemia	7 (5.51)	2 (8.70)	1.63 (0.32—8.40)	0.558		
Endocrine, nutritional and metabolic diseases	31 (24.41)	5 (21.74)	0.86 (0.29—2.51)	0.783		
Diabetes mellitus	20 (15.75)	0 (0.00)	—	0.044[b]		
With complications	8 (6.30)	0 (0.00)	—	0.609[b]		
Diseases of the circulatory system	38 (29.92)	5 (21.74)	0.65 (0.23—1.88)	0.427		
Heart failure	3 (2.36)	0 (0.00)	—	1.000[b]		
Diseases of the respiratory system	35 (27.56)	11 (47.83)	2.41 (0.97—5.96)	0.057		
Respiratory tract infection	21 (16.54)	8 (34.78)	2.69 (1.01—7.15)	0.047	1.41 (0.49—4.04)	0.185
Respiratory failure	2 (1.57)	2 (8.70)	5.95 (0.79—44.59)	0.083	2.12 (0.21—20.96)	0.169
Diseases of the digestive system	17 (13.39)	3 (13.04)	0.97 (0.26—3.62)	0.965		
Diseases of the genitourinary system	35 (27.56)	8 (34.78)	1.40 (0.55—3.60)	0.482		
Urinary tract infection	18 (14.17)	4 (17.39)	1.27 (0.39—4.18)	0.689		
Renal failure	15 (11.81)	4 (17.39)	1.57 (0.47—5.25)	0.462		
Diseases of the nervous system	19 (14.96)	0 (0.00)	—	0.046[b]		
Diseases of the skin and subcutaneous tissue	11 (8.66)	3 (13.04)	1.58 (0.41—6.18)	0.509		
Diseases of the musculoskeletal system and connective tissue	17 (13.39)	0 (0.00)	—	0.076[b]		
External causes of morbidity	44 (34.65)	4 (17.39)	0.40 (0.13—1.24)	0.112		
Injury, poisoning and certain other consequences of external causes	40 (31.50)	4 (17.39)	0.46 (0.15—1.43)	0.180		
Systemic infection or organ failure	24 (18.90)	11 (47.83)	3.93 (1.55—9.98)	0.004	4.21 (1.38—12.81)	0.032
Immunocompromised status	29 (22.83)	9 (39.13)	2.17 (0.85—5.53)	0.104		
Healthcare exposure						
Emergency admission	98 (77.17)	20 (86.96)	1.97 (0.55—7.11)	0.299		
Admission from healthcare facilities	13 (10.24)	3 (13.04)	1.32 (0.34—5.04)	0.689		
Surgical specialty	60 (47.24)	9 (39.13)	0.72 (0.29—1.78)	0.474		
TAR (days), median (IQR)	5 (1—25.5)	13 (2—20.5)	1.01 (0.98—1.03)	0.593		
HDU stay	47 (37.01)	8 (34.78)	0.91 (0.36—2.30)	0.839		
Duration of HDU stay (days), median (IQR)	0 (0—2.5)	0 (0—2.5)	1.01 (0.97—1.06)	0.523		
ICU stay	33 (25.98)	9 (39.13)	1.83 (0.72—4.63)	0.201		
Duration of ICU stay (days), median (IQR)	0 (0—0)	0 (0—0.5)	1.02 (0.94—1.11)	0.636		
Hospitalization	53 (41.73)	11 (47.83)	1.28 (0.53—3.12)	0.587		
Duration of hospitalization (days), median (IQR)	17 (1—39)	18 (9—38)	1.00 (0.98—1.02)	0.799		

Table II (*continued*)

Characteristics	Survivor (%)[a] (N=127)	Non-survivor (%)[a] (N=23)	Univariate		Multi-variate	
			OR (95% CI)	P-value	aOR (95% CI)	P-value
Hospital transfer	23 (18.11)	4 (17.39)	0.95 (0.30–3.06)	0.934		
Ward transfer	65 (51.18)	15 (65.22)	1.79 (0.71–4.51)	0.218		
Invasive procedures						
Any	52 (40.94)	12 (52.17)	1.57 (0.65–3.84)	0.319		
Centesis	7 (5.51)	3 (13.04)	2.57 (0.61–10.78)	0.196		
Ectomy	15 (11.81)	3 (13.04)	1.12 (0.30–4.23)	0.867		
Transplantation	4 (3.15)	0 (0.00)	–	1.000[b]		
Catheterization	15 (11.81)	2 (8.70)	0.71 (0.15–3.34)	0.666		
Urinary catheter	3 (2.36)	1 (4.35)	1.88 (0.19–18.89)	0.592		
CVC	12 (9.45)	2 (8.70)	0.91 (0.19–4.38)	0.909		
Dialysis or drainage	6 (4.72)	1 (4.35)	0.92 (0.11–7.99)	0.937		
Endoscopic operation	8 (6.30)	3 (13.04)	2.23 (0.55–9.13)	0.264		
Invasive ventilation	6 (4.72)	2 (8.70)	1.92 (0.36–10.16)	0.443		
Other surgical procedures	17 (13.39)	3 (13.04)	0.97 (0.26–3.62)	0.965		

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; CPO, carbapenemase-producing organisms; IQR, interquartile range; ICU, intensive care unit; HDU, high dependency unit; TAR, time at risk; CVC, central venous catheter; –, not applicable.

[a] Number of survivors/non-survivors with the characteristic (percentage of survivors/non-survivors with the characteristic among all the survivors/non-survivors investigated), unless stated otherwise.

[b] Fisher's exact test.

quarters of patients audited had undergone CPE screening in line with the national policy (76.1%) [14].

Similar to English data [15], the 'big five' carbapenemases (VIM, NDM, KPC, OXA-48 and IMP) accounted for 96.7% of all 243 CPO isolates. In contrast to a London study that reported 34% carbapenem-resistant non-fermenters [16], only 15.2% of all the CPO isolates in Scotland were non-fermenters. This study highlights another urgent public health threat, namely the presence and transmission of CPO in the community. The overall CA rate was 29.4% (62/211) and the incidence of CA cases increased significantly over time ($P<0.001$). However, the CA rate could have been overestimated due to possible long-term persistence as stated above (up to 740 days) while using 1 year from last hospitalization in the definition of CA. A scoping review found that the percentage of either CA or community-onset carbapenemase-resistant Enterobacterales ranged from 0.04% to 29.5% [17], while a study reported the rate of community-onset infections caused by CPE as 22.9% [18]. Moreover, 69.4% of the 62 CA cases in the present study were NDM/OXA-48 producers. The occurrence of OXA-48 producers in the community is often a consequence of importations from endemic countries [19]. Also, it has been reported that many NDM-1-positive patients in the UK had travelled to India or Pakistan within the preceding year, or had links with these countries [20]. Unfortunately, travel information is not available in this study. Although enhanced data in the electronic reporting system submitted to the AMRHAI Reference Unit include foreign travel, such information is filled in retrospectively on a voluntary basis following confirmation of carbapenemase production, and only 26% of records included foreign travel information [15]. As travel is known to be associated with increased risk for CPO, it is essential that information on travel history, particularly foreign travel to endemic countries, should be collected routinely in the community and on admission to healthcare facilities.

Both host- and pathogen-related factors were reported to be drivers of adverse outcomes. This study found that advanced age, presence of carbapenemase-producing non-fermenters, malignancy, respiratory tract infection, and systemic infection or organ failure were associated with overall 30-day mortality. Advanced age has been reported to be a risk factor for mortality by many researchers, as this group represents a vulnerable population for drug-resistant pathogens [21–23]. Patients with malignancies usually have more frequent exposure to health care such as immunocompromised therapy (radiotherapy and chemotherapy), invasive procedures (biopsies, bone marrow and spinal puncture) and longer hospitalization. Respiratory infection has been described as a risk factor for 30-day mortality in other studies [24,25]. Mucosal barrier injury in the respiratory tract and altered lung tissue would decrease the capacity for bacterial clearance and increase the probability of bacterial colonization and/or infection. Multi-variate analysis revealed that both carrying non-fermenters and systemic infection or organ failure were independently associated with 30-day mortality. To the authors' knowledge, only one study has investigated the association between organisms and mortality, and this study did not find any particular organism to be linked to mortality [26]. Both virulence status and antimicrobial resistance may account for this. First, some studies have demonstrated that virulence determinants of *Pseudomonas* spp., such as the secretion of toxins and elastase activity, could enhance pathogenicity against host defence mechanisms, thus having an unfavourable impact on outcome. In addition, biofilm formation on the lumen of the respiratory tract could result in a higher risk of mortality by posing greater resistance to antibiotics [27,28]. Second, carbapenem resistance in non-fermenters usually stems from a combination of beta-lactamases, porin mutations and efflux pump overexpression, conferring reduced susceptibility to antibiotics and implying fewer treatment options and more treatment failure [29]. Systemic infection or organ failure is a surrogate marker of critical illness which has been widely reported as a predictor of poorer outcome [21,22,27,30]. Aggressive therapy and infection prevention and control measures should be initiated rapidly in this population.

This study had a few limitations. First, no classification of infection and colonization was made due to lack of clinical symptoms and laboratory testing data. Second, data on comprehensive antimicrobial susceptibility and antimicrobial treatment in hospital at individual level were not available. Third, no genomic data were available to identify possible clonal spread, outbreak and virulence. Further molecular study is warranted to better understand the phylogeny and pathogenicity of local CPO isolates.

In conclusion, the incidence of CPO in Scotland is relatively low but is increasing rapidly. Awareness is required that patients of advanced age, patients with systemic infection or organ failure, and patients presenting with non-fermenters are at higher risk of death from CPO. There is a need to continue the existing Scottish CPE surveillance programme, and infection prevention and control measures for both Enterobacterales and non-fermenters warrant further consideration in both health care and the community to help control the spread of CPO. The findings of this study will also inform other countries with similar epidemiological situations.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.01.028.

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